

FIG. I

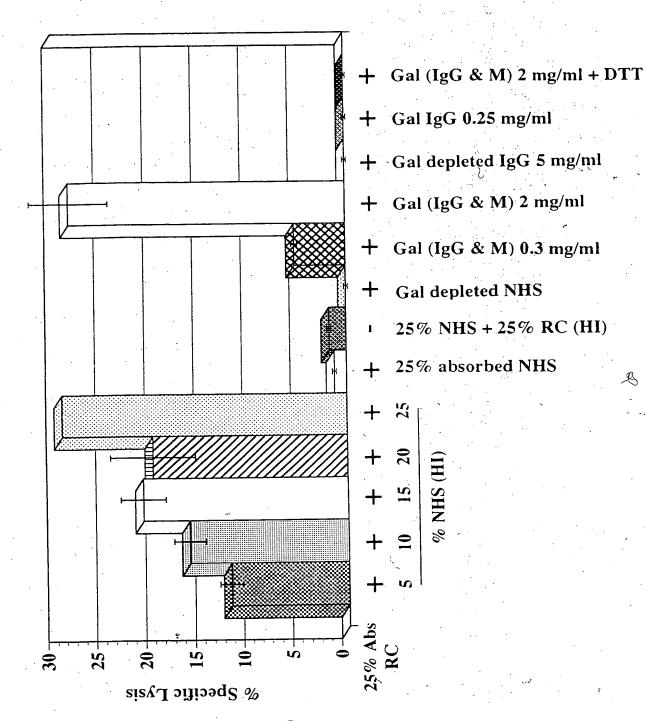
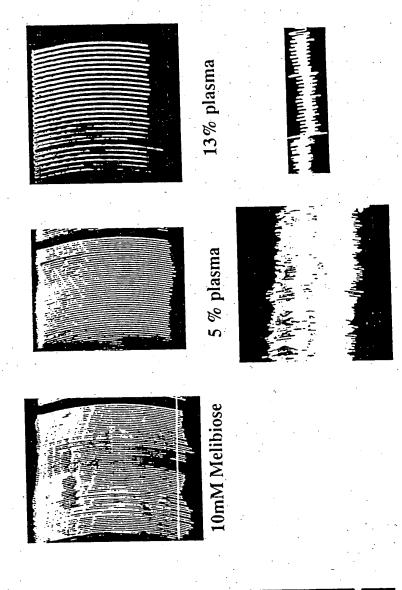


FIG. 2

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Baseline

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	•	•	6.			
50 50	100 100 100	150 150 150	200 200 200	250 250 250	300 300 300	350 350 350
CAGCGCCGC	9009909900	CGCGGGGCTC	9999009009	CGGATCAGGG CCTAGCCCTG	AGGAACTTGC CTTGGAATGA	1 T Exon 2 ACGGAGTCAG TGGGAGTTGG
GCCGCTGCC	GGAGGAGCGC	CCGGCACGCC	AGCCGAGGAC	CCAGCTTCTG	GCCAGCCAGC TGTCCCCAAG AGGAACTTGC ACCTTCCCTT GTAGACTCTT CTTGGAATGA	Exon 1 Exon 2
GGCCGAGCTG GGAGCGTCGA	222222222	ACACCCGCC	CTGTTCCGGC	CCCAGCGCGC		 CGAGACACTT GACCTCGCGC
	GCGCCCCTGC	GCCGACGGGA GCGCAGCGGC	AGCGCGCCGA	AGCCGAGGCG CCGGCCAGCC	TCCTCAAGTG	 CACGGAAAGA TTCTGCTGAA
900999900	CGGCTCCCTC	GCCGACGGGA	GGGAGGAGGC	AGCCGAGGCG	AAACCACGTG	
ਜਜਜ	51 51	101 101 101	151 151 151	201 201 201	251 251 251	301 301 301
PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS

# FIG. 4A

•							
	400 400 400	450 450 450	500 500 500	550 550 550	009	650 650 650	700
	T TCTGCAGAGC T TCTGCAGAAC T TCGGCAGGCC	G GGGGAGAGA 'A GGAGGAGAGA 'G GAGGGAACAC	  T TACCCCAGTC	 	 	n 3 Exon 4 GAGAAAA GAGAAAA  A CAGGAGAAAA	T TGTCTCAACT T TGTCTCAACT T TGTCTCAACC
	CCTGCCTCCT CCTGCCTCCT CCTGCCTCCT	TTTTACTCTG TTTTACTCTA GTTTGCTTTG	 	  CTGGACCTAA	 	Exon	CAATGCTGCT CAATGCTGGT TGATGCTGAT
	TCCCAGC TCTGCTGAGC	TTCGCC TACTTTTGCC TTGCTTTGCT	  TTGAACTCAA	 		 	GTGGTTCTGT GTGATTCTGT GTAATCCTGT
	CTTCCTTTCC	AGAACTT-GT AGAACTT-GG AGAAGCTCGG	2 Exon 3 GAG GAG GAGGCTGACT	 AAAGGCCTGT	  TTCAAGATCT	  ACAAGTCTTC	CAAAGGAAGA CAAAGGAAAA CAAGGGAAAA
	AAGGCTGCAC	AGAGCTCACT GGAGCTCAGT AGAGCTCGAC	Exon AGCAGAGGAT AGCAGACGAT AGCTGACGAT	 TCCTGGAATT		 	TAATGAATGT TAATGAATGT TAATGAATGT
	351 351 351	401 401 401	451 451 451	501 501 501	551 551 551	601 601 601	651 651 651
	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS

# F16.4B

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	•					•
750	800	850	006	950	1000	1050
750	800	850		950	1000	1050
750	800	850		950	1000	1050
GTTCTTTGTT	GCTCAGAGGG	CAGTTACCAC	AAGAAGACAA	Exon 8  AAACGCCCAG  AAACGCCCCG  AAACGCCCCG	GGAAGGCACT	GCCAAACAGA AAATTACCGT
GCTCTTTGTT	AGCATTCAGA	GTTACCAT	ACGAAGACGA		GGAAGGCACT	GCCAAGCAGA AAATTACCGT
GCTCTTTCTT	AGATGGCAGA	CAGTTATCAA	GAGATCGCAT		GGAAGGCACT	GCCACACAGA AACTCACTGT
Exon 4 Exon 5  ATACATCAAC AGCCCAGAAG  ATATATCCAC AGCCCAGAAG  ATATGTCAAC AGCCCAGACG	Exon 5 Exon 6 CAGTCAAAAA ACCCAGAAGT TGGCAGCAGT CCATCAAGAA ACCCAGAAGT TGGTGGCAGC CACACAAAAA TTCCAGAGGT TGGTGAGAAC	Exon 6   Exon 7  TGGTTTAACA ATGGGACTCA CAGTTACCAC  TGGTTTAACA ATGGTTACCAT  TGGTTTAAAA ATGGGACCCA CAGTTATCAA	GAACAAAGAA AAGAAGACAA GAACAAAGAA ACGAAGACGA GGTAGAAATG GAGATCGCAT	Exon 7 T TAATCCTGAG CAACCCATTT CAATCCAAAG	CAGTGGTATG CAGTGGTGTG CGATTGTGTG	
Exon 4 ATACATCAAC A ATATATCCAC A ATATGTCAAC A	Exon 5 Exon 6 CAGTCAAAA ACCCAGAAGT CCATCAAGAA ACCCAGAAGT CACACAAAAA TTCCAGAGGT	Exon 6  TGGTTTAACA ATGTTTAACA ATGTTTAAAA ATG	CAACGAAAAG CGAAGAAAAG GAGAGAAAAG	TGGACTGGTT CGGACTGGTT GGGACTGGTT	TGGAAGGCTC TGGAAGGCTC TGGAAGGCGC	TAATTATTAT CAATTATTAT AAAGTACTAC
TGTTTTGGGA	Exon 5 T CAGTCAAAAA CCATCAAAAAA CACACAAAAAA	-TTTCCGAGC	ACGCTATAGG	CAGAGGAGAG CTTCCGCTAG	CATAACCAGA	CCGTCTTAGA
TGTTTTGGGA		GCTTCCGAGA	GAGACATAAA	AAGCAAG CTTAAGCTAT	CATGACGAAG	CCGTCTTAGA
TGTTTTGGGA		GTTCCCAAGC	TAGAAGGACG	TGAAGAG CCTCAGCTAT	AGTGACCCCG	CTCTGCTGGA
GTAATGGTTG	CTGGATATAC	GCTGGTGG	GAAGAAGAAG	CAGAGGAGAG	AGGTCGTGAC	TACAACAGAG
GTCATTGTTG	CTGGATAAAC	AGGGCTGGTG	GAAGAAGATG	AAGCAAG	AGGTTGTGAC	TACAACAGAG
GTGGTTGTCG	GTGGATATAT	AGGACTGGTG	GAAGACAACG	TGAAGAG	ATGTTTTGAC	TATGACACAG
701	751	801	851	901	951	1001
701	751	801	851	901	951	1001
701	751	801	851	901	951	1001
PGTCD	PGTCD	PGTCD	PGTCD	PGTCD	PGTCD	PGTCD
BOVGSTA	BOVGSTA	BOVGSTA	BOVGSTA	BOVGSTA	BOVGSTA	BOVGSTA
MUSGLYTNS	MUSGLYTNS	MUSGLYTNS	MUSGLYTNS	MUSGLYTNS	MUSGLYTNS	MUSGLYTNS

# F16.4C

### 1200 1200 1300 1300 1100 1150 1300 1350 1400 1400 TAGAGCTGGG TAGAGTTGGG TACTTGGAGG TACTTGGAGG TGCACCTGAA AAGAGGTGGC TACTTAGAAG CCCAGTCATC TCGGGTCATA AAGAGGTGGC CATCCTGGCC CATTGTGGCC TGGACCAGGT CAAAGTCATC AAGAGGTGGC CATCCTGGCC TGGATCAAGT GTGGCTCAGC GTGGCCCAGC TGGATCAGGT GTAGCACAGC GTGTTTGCTG TGGGAAAGTA CATTGAGCAT CATTGAGCAT TGGTTGGCCA CAAGTCCGAG CAAGCCTGAG CAGGTCTGAG CATTGAGCAT TGGTTGGCCA TGGTGGGCCA ATGCCTTTGA ATGCCTTTGA ATGCCTGTCG TCGGGGAGCA TCGGGGAGCA TTGGGGAGCA TGCATGGACG TGCATGGATG TGCATGGACG GGCCAGTCG GGGCGAGTCG GGCCAGCTG Exon 9 TCGGAAGATA TGGTGGATGA TATCTCCAGG TITIACGICA IGAIAGAIGA CACCICCGG TGTTTGAGAT GTTTTCGCCG TCGGAAGATA ACATACTTCA AAGCACTTCA ATGTACTTCA TGTCTCCAGG TCTTTGAGAT AACTTTGGGG TGGAGACCCT TGGAGACCCT TGTTTAAGAT ATGAAGACCA ATGAAGACTA ATGAAGACCA CTTCCTCTTC TGGAAACTCT CTTCCTCTTC CTTCCTTTTC Exon 8 ATCTGCAAAT TCCTTTAAAG TCCTTACAAG AAGTTTGGGG AACTTCGGGG GTTTTTGCTG GTCTGCTAAT GTCTGCTGAC TGGTAGATGA TCCTTCAAAG CATGATGCGC CATGATGCGC CATGATGCGC ACGAGGTCGA ACGAGGTGGA ATGAGGTTGA TCCTCTGCGT AAGACATCAG CTTCCAAAAC CTTCCAAGAC GGGCTTGACG CGGCCTGACG GGGCTGACA AGTTCTTAAT AGTTCTTAAC ACTTTCTGGA TTTTACATCA TTTTATATCA TCCTCTGCGC CCCTCTACAT AGGACATCAG AGGATATCAG CACATCCAGC CACATCCAGC CACATCCAGC CTTTCAAGAC 1101 1101 1101 1251 1051 1051 1151 1151 1151 1201 1201 1201 1251 1351 1351 1251 1301 1301 1301 1351 MUSGLYTNS MUSGLYTNS MUSGLYTNS MUSGLYTNS MUSGLYTNS MUSGLYTNS MUSGLYTNS BOVGSTA BOVGSTA BOVGSTA BOVGSTA BOVGSTA BOVGSTA BOVGSTA PGTCD PGTCD PGTCD PGTCD PGTCD PGTCD PGTCD

# FIG. 4D

1450	1500	1550	1600	1650	1700	1750
1450	1500	1550	1600	1650	1700	1750
1450	1500	1550	1600	1650	1700	1750
CTACGAGAGG	ATTTTATTA	AACATCACTC	CATAGAAGCC	TCAACAAACC	ATAGGCATGT	AGAGTATAAT
CTACGAGAGG	ATTTTTATTA	AACATCACCC	CATAGAAGCC	TCAACAAACC	ATAGGCCTAC	AGAGTATAAT
CTATGAGAGG	ATTTTTACTA	AACCTCACCA	CATAGAAGCC	TCAACAAACC	ATAGGCCTGC	AGAGTATAAT
ACGAGTTCAC	GGCCAGGGGG	TCAGGTTCTA	AGGAAAATGA	TATTTCCTTC	GGATTATCAT	GGCAGAAAAA
ATGACTTCAC	GGCGAAGGGG	TCAGGTCCTT	AGAAAAATGA	TATTTCCTTC	GGATTATCAC	GGCAGACAAA
AGAAGTTCAC	GGAGAGGGGG	TCACATTCTC	AGAAACATGA	TACTTCCTTT	GGACTATCAG	GGCAGACAAA
GCACATCCTG ACGAGTTCAC	CATTCCGTTT	GAACACCCAC	CTCCAGGACA	TCTAAACAAG	AATACTGCTG	AAGATAGCTT
GCAGATCCCA ATGACTTCAC	CATTCCCTTC	GAACACCCAC	CTCAAGGACA	TCTAAACAAG	AATACTGCTG	AAGATGTCTT
GCCAGTCCCG AGAAGTTCAC	CATTCCATTC	GAACGCCTAC	CTCCAGGACA	CCTCAACAAA	AGTATTGCTG	AAGGTAGCTT
GTGGTACAAG	CCGCAGCCTA	ATTTTGGGG	CAAGGGAATC	ATGAAAGCCA	TTATCCCCAG	TAGGATTGTC
GTGGTACAAG	CTGCAGCATA	ATTTTTGGGG	CAAAGGAATC	ATGAAAGCCA	TTATCCCCGG	TAAGCTTGTC
GTGGTACAAG	CGGCCGCGTA	ATTTTTGGAG	TAAGGGGATC	ATGAGAGCCA	CTATCTCCAG	TAAAAGTGTC
TACAGGCCTG	CGGAAGGAGT	CCACGCAGCC	AGGAGTGCTT	GAGTGGCATG	CACTAAAATC	CTGTGGATAT
TACAAGCCTG	CGGAAGGAGT	CCATGCAGCC	AGGAATGCTT	CAATGGCATG	TACTAAAATC	CTGCGGATAT
TCCAGGCCTG	CGGGAACTGT	CCACGCGGCC	GGGAGTGCTT	CAGTGGCATG	CACTAAAATC	CTTCAGATAT
1401	1451	1501	1551	1601	1651	1701
1401	1451	1501	1551	1601	1651	1701
1401	1451	1501	1551	1601	1651	1701
PGTCD	PGTCD	PGTCD	PGTCD	PGTCD	PGTCD	PGTCD
BOVGSTA	BOVGSTA	BOVGSTA	BOVGSTA	BOVGSTA	BOVGSTA	BOVGSTA
MUSGLYTNS	MUSGLYTNS	MUSGLYTNS	MUSGLYTNS	MUSGLYTNS	MUSGLYTNS	MUSGLYTNS
•		•				

1800 1800 1800	1850 1850 1850	1900 1900 1900	1950 1950 1950	2000	2050 2050 2050	2100 2100 2100
TTTTCTGAAT ATTTCTGAAT ATGGAAAC	CACTTAA CACTTAA CAACACTTGA	CACAGTAA-G CACAGCAA-A TACCATGGCA	GGGAGAATGA GGGAGAATGA GTGAGAAAGA	TTACCTATTT TTATATATTC	 CC TTGACAAAGG	
TTGGTTAGAA ATAACATGTG ACTTTAAATT GTGCCAGCAGGTGGTTAGAA ATAATGTGTG ACTTT GTGCCAGTACTTGGTTAGAA ATAATGTGTG ACTTCAAATT GTGStop	CTACTTCCTC AGAGAAGTAG CTACTTCCTC AGAAAAGTAA CTAATTCCTC AAACAAGTAG		AACTTTGAGC CTTGTCAAAT GGGAGAATGA AACTTTGAGC CTTGTAATAC GGGAGAATGA CACCTTGAGC CT-GTAATAT GTGAGAAAGA	TGTAAATTCC CAGTGATTTC TGTAAATTCC CAGTGATTTC TATAAATTCT CAATGATTTC	ATCAGTTGAA CAAAATTAAT	GCCGGAAACT TCTTCCCAGT CTGTCATACA ATTCACCACT
TTGGTTAGAA ATAACATGTG ACTTTAAATT GTGCCAGCA GTGGTTAGAA ATAATGTGTG ACTTT GTGCCAGTA TTGGTTAGAA ATAATGTG <u>TG A</u> CTTCAAATT GTG		CTAACAAAA- CTAACAAAA- CAATCAAAAC	AACTTTGAGC AACTTTGAGC CACCTTGAGC		TGGATACACC	TCTTCCCAGT
ataacatqtg ataatgtqtg ataatgtq <u>tg</u> Sk	ATTACTCTGG ATTATTCTGG ATTACTCTGG	TAAAAAAATA AAAAAAAATA TAAAAGAA-A	TCTCCTTGC TTCTCCTTGT TTCTCCT-GA	TAATCAGA TAATCAGA AGTAATCAGG	TTGGTTGTGG GGGCGGGGAA TGGGTCTTGG GAAAACTTGA	GCCGGAAACT
TTGGTTAGAA GTGGTTAGAA TTGGTTAGAA	TTGAAAGAGT TTGAGAGAGT TTGACACT	TTTTAACTTT TTTTAACTTA TTTCAACTTT	TACATATTAT TACATATTAT AACAGATGAT	CTCTGTGG ACCTGTGG GTCTATGGCA	TTGGTTGTGG TGGGTCTTGG	AAAAGCAGAT
1751 1751 1751	1801 1801 1801	1851 1851 1851	1901 1901 1901	1951 1951 1951	2001 2001 2001	2051 2051 2051
PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS

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2200 2200 2200	2250 2250 2250	2300 2300 2300	2350 2350 2350	2400 2400 2400	2450 2450 2450
ATGGAGATTC	TAAGGATGCC	CGCTGGCAGT	GGAGGCAGAG	GGAAAAATCA	ATTGAACTGA
		GCTCCAGGAG		TCAGAGTCCA	GGGGTTGGTG
	TTGCAGCCAG	AAAGCTGATG	GTTTCTGTCC	TGGCACATGT	CATAGGACTT
		TCAGTCTGTA	CTAGGCTATT	GGTACTTTGG	AGGGTGACCA CTTAGAGGGA
TGGACGGCTC	TAAAGCAACC	AATGTGACCA	CCAGGCCCCA	AGTGCCAATA	AGGGTGACCA
2151 2151 2151	2201 2201 2201	2251 2251 2251	2301 2301 2301	2351 2351 2351	2401 2401 2401
PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS
	2151	2151 2151 2151 2151 TGGACGCTC CATCCTTTG GCTTCATTAT CTTCCTCCTC ATGGAGATTC 2201 2201 2201 2201 2201 2201 2201 220	2151 2151 2151 2201 2201 2201 2201 2201	2151 2151 2151 2151 2201 2201 2201 2201	2151 NS 2151 TGGACGCTC CATCCCTTTG GCTTCATTAT CTTCCTCCTC ATGGAGATTC 2201 NS 2201 TAAAGCAACC CAGAGAGCT TTGCAGCCAG AGACCTTTAA TAAGGATGCC 2251 NS 2251 NS 2251 NS 2251 NS 2301 NS 2301 S301 S301 S301 S301 NS 2301

# FIG. 4G

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	•					
2500 2500 2500	2550 2550 2550	2600 2600 2600	2650 2650 2650	2700 2700 2700	2750 2750 2750	2800 2800 2800
TCTTCAGGAT GACTAACAGC AGGAATTGAA	GTTCATTTTG TTTTGCCCAA ATTGTATTCA TGCTGTTAGC	GGGAAGGAGA	AAGACAATCT	GAGTTCCTCA	TGGAGCAGGT GACTGAAGAC	ACTATGCAAG
GACTAACAGC	ATTGTATTCA	GAGAGGGTGT GACTGTATCA	GTACCTCAGC GGACTGAGGA CCAGCACCCT ATTATATCAG AAGACAATCT	CTGAACCTCC	TGGAGCAGGT	CTCATTTCC CTGCTCTAGT ACTATGCAAG
TCTTCAGGAT	TTTTGCCCAA		CCAGCACCCT	ACAACCTGCT	GGGCCTGTA	
CAGACAGCTT	GTTCATTTTG	TTGTGTGTT GAGCCCTGTG	GGACTGAGGA	GGTCCTACCT	TTCCAGTGTG	GTCACATGAC
GTTACAAACA	TGGAAAGTGT	TTTGTGTGTT	GTACCTCAGC	CTCATCATCA	GCCCATCGTG TTCCAGTGTG	AAAGCCCCCT
2451 2451 2451	2501 2501 2501	2551 2551 2551	2601 2601 2601	2651 2651 2651	2701 2701 2701	2751 2751 2751
PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS
						•

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2850 2850 2850	2900 2900 2900	2950 2950 2950	3000 3000 3000	3050 3050 3050	3100 3100 3100
ACCGACTTTA	ACTACAACGG AGCTGCTGAA GGTTCTGTTC	CTCAACCTAT	CAGGTGTCCC	GTAACAGTAG	
CAACATAGGA	AGCTGCTGAA	ATAGGTGGTT	GACCCTTTCA	ACTCTGACTG	ATAATTCTGG
ATGTACTGGA	ACTACAACGG	GAGCCCCTGT	AGTGTTAAAT	AGATATTTCC	AGCAAGGGAA
AGCCAGCCAG	TGGCAATGGG AGCCGCAGTC	GAGCCTGCAG	GGGTCGCGAC CCCTTTGGGA AGTGTTAAAT GACCCTTTCA CAGGTGTCCC	TAAAAAACAT	
TGTGACAGCC AGCCAGCCAG ATGTACTGGA CAACATAGGA ACCGACTTTA	TGGCAATGGG	CCCGCTCTGA GAGCCTGCAG GAGCCCCTGT ATAGGTGGTT CTCAACCTAT	GGGTCGCGAC	CTAAGACGGT TAAAAACAT AGATATTTCC ACTCTGACTG	CAGAATTACA
2801 2801 2801	2851 2851 2851	2901 2901 2901	2951 2951 2951	3001 3001 3001	3051 3051 3051
PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS	PGTCD BOVGSTA MUSGLYTNS

# F16.4

	20	20	20
<b>x</b> 6	1 MNVKGRVVLS MLLVSTVMVV FWEYINSPEG SLFWIYQSKN PEVG-SSAQR 50	PEVGGSSIQK	1 MNVKGKVILL MLIVSTVVVV FWEYVNSPDG SFLWIYHTKI PEVGENRWQK 50
Ex5 VEx6	SLFWIYQSKN	SLFWINPSRN	SFLWIYHTKI
$Ex4 \bigvee Ex5$	FWEYINSPEG	FWEYIHSPEG	FWEYVNSPDG
	MLLVSTVMVV	MLVVSTVIVV	MLIVSTVVVV
	MNVKGRVVLS	1 MNVKGKVILS MLVVSTVIVV FWEYIHSPEG SLFWINPSRN PEVGGSSIQK	MNVKGKVILL
	⊣	ਜ਼	<b>←</b> 1 ·
.*	$\overline{\Box}$	$\Box$	1]
	PGT[Frame	BGT[Frame	MGT[Frame

æ	е 100	ь 100	ים 100 מי
$Ex7 \setminus Ex8$	DWFNPEKRF	DWFNPFKRF	DWFNPKNRF
	EDNRGELPLV	ED-ESKLKLS	DWWFPSWFKN GTHSYOEDNV EGRREK-GRN GDRIEEPQLW DWFNPKNRPD 100
,	AIGNEKEORK	DINEEKEORN	EGRREK-GRN
Ex6 Ex7	GTHSYHEEED	GYHEEDG	GTHSYOEDNV
Ex6	GWWFPSWFNN GTHSYHEEED AIGNEKEQRK EDNRGELPLV DWFNPEKRPE 100	GWWLPRWFNN GYHEEDG DINEEKEORN ED-ESKLKLS DWFNPFKRPE 100	DWWFPSWFKN
	] 51	] 51	. 51
	PGT[Frame 1	3GT[Frame 1	MGT/Frame l

AV GRYIEHYLEE 150	AV GRYIEHYLEE 150	1 VLTVTPWKAP IVWEGTYDTA LLEKYYATQK LTVGLTVFAV GKYIEHYLED 150
ITVGLTVF	ITVGLTVF	LTVGLTVF
VLDNYNAKQK	VLDNYYAKQK	LLEKYYATQK
VVWEGTYNRA	VVWEGTYNRA	IVWEGTYDTA
VVTITRWKAP	VVTMTKWKAP	VLTVTPWKAP
PGT[Frame 1]101	BGT[Frame 1]101	MGT[Frame 1]101
	me 1]10:	me 1]10; me 1]10;

]]	1]151 FLTSANKHFM VGHPVIFYIM VDDVSRMPLI ELGPLRSFKV FKIKPEKRWQ 200	Ϊ.
PGT[Frame 1]151	]	Ϊ.

# FIG. 5A

250

ETLGESVAQL

DQVFQDKFGV

EVDFLFCMDV

GEHIVAHIQH

DISMMRMKTI DISMMRMKTI

1]201

BGT[Frame PGT[Frame

1]201

GEHILAHIQH

EVDFLFCMDV DQVFQNNFGV ETLGQSVAQL 250

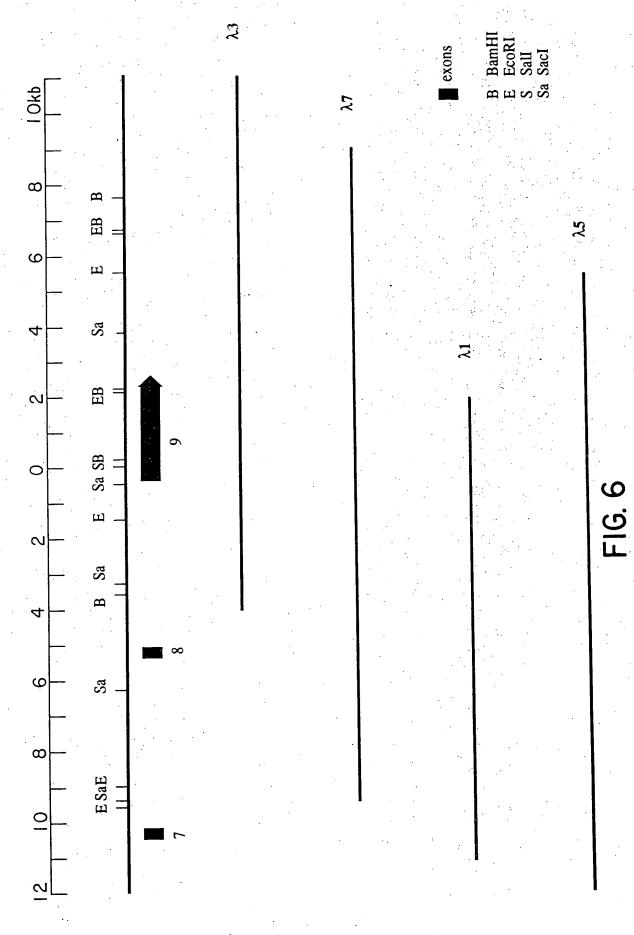
QTKEYNLVRN NV\*

SDIKSVKVAW

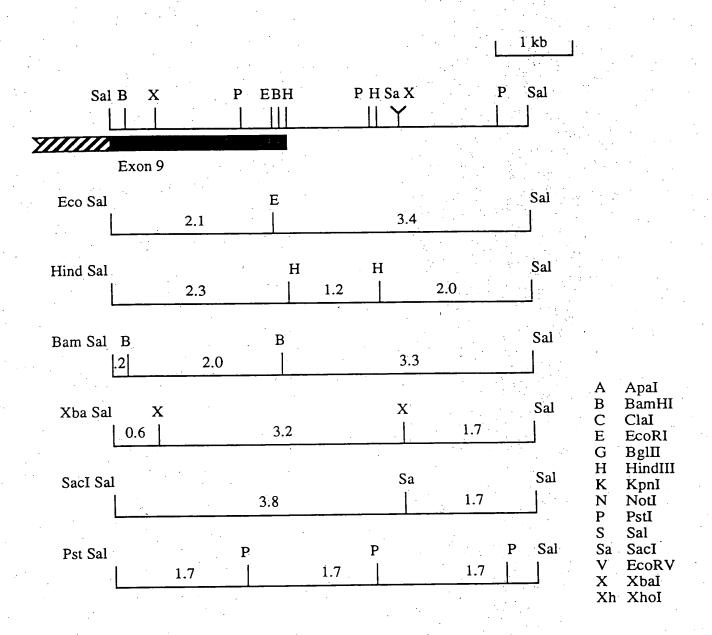
1]351

MGT[Frame

# F16.5B



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No sites for: BglII, Nde, PvuI, Xho, Kpn, SacII, EcoRV, Sma, Cla, Apa, Not

pBS+KS: .... SacI SacII Not Xba Spe Bam Sma Pst Eco RV Hind Cla Sal Xho Apa Kpn ....

FIG. 7

07039-473002

1 kb E X Sa V Sal B H Sa G G Sal Exon 9 Sal Ε Eco Sal 1.5 2.5 Sal Hind Sal Η 3.3 0.7 Sal Bam Sal В 3.6 0.4 X Sal Xba Sal 3.1 0.9 Sa Sal Sa SacI Sal ApaI BamHI 0.5 \_ 2.7 0.7  $\mathbf{B}$ C ClaI E. EcoRI Sal G Sal G G BglII -2.0 1.0 1.0 Η HindIII K KpnI N Not Sal EcoRV Sal-P PstI 3.9 S Sal Sa SacI

No sites for: Nde, PvuI, Xho, Kpn, SacII, Sma, Cla, Apa, Not

Unmapped sites for: Pst, PvuII

### pUBS:

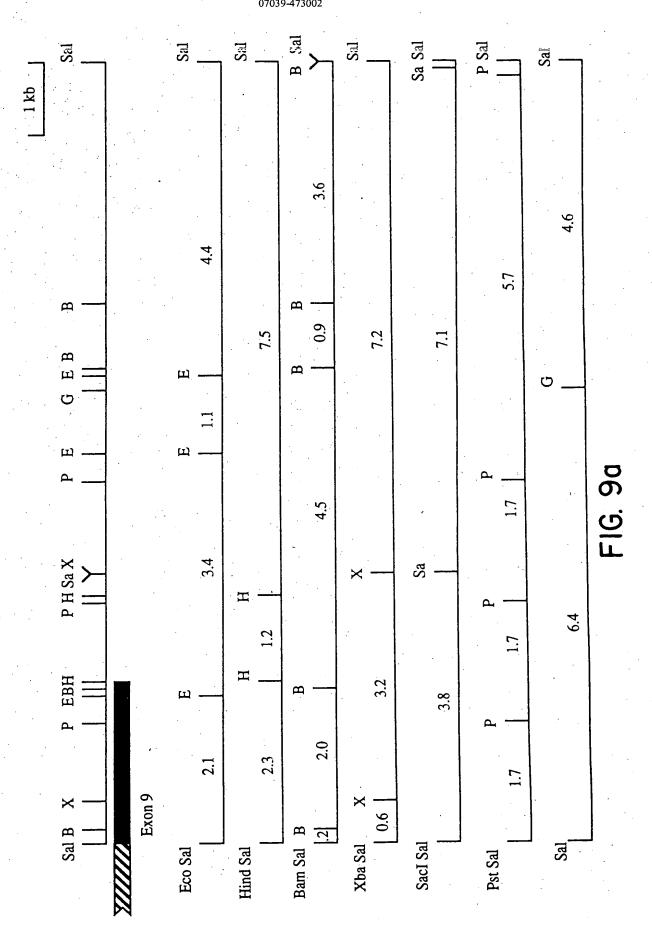
.... SacI SacII Not Xba Spe Bam Sma Pst Eco RV Hind Cla Sal Xho Apa Kpn ....

V.

X XbaI Xh XhoI

EcoRV XbaI

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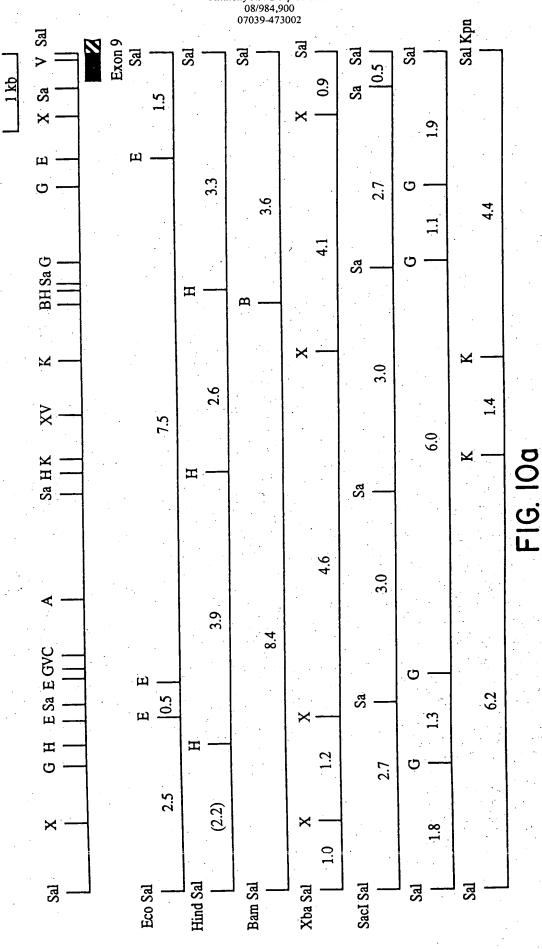
BglII HindIII Kpnl Notl Pstl Sal Sacl EcoRV Xbal EcoRI XX < Sa S > XX

FIG. 9b

.... SacI SacII Not Xba Spe Bam Sma Pst Eco RV Hind Cla Sal Xho Apa Kpn ....

No sites for: Xho, Kpn, SacII, Sma, Cla, EcoRV, Apa, Not, Pvul, Nde

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Sal Apa Sal Sal Apal BamHI Clal EcoRI BgIII HindIII XX<Son ZXXIIOECEA 4.6 8.6 ----SacI SacII Not Xba Spe Bam Sma Pst Eco RV Hind Cla Sal Xho Apa Kpn----3.8 No sites for: Xho, SacII, Sma, Not 4.3 3.4 3.4

**RV** Sal

Sal

Sal

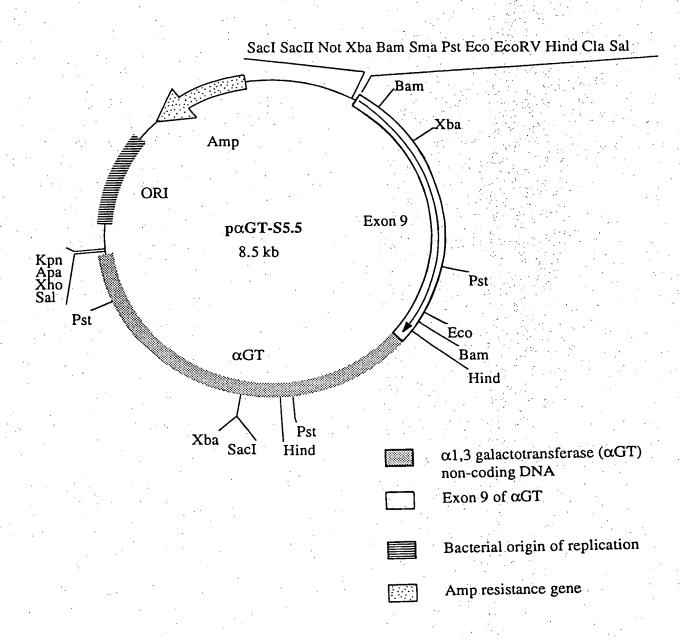


FIG. II

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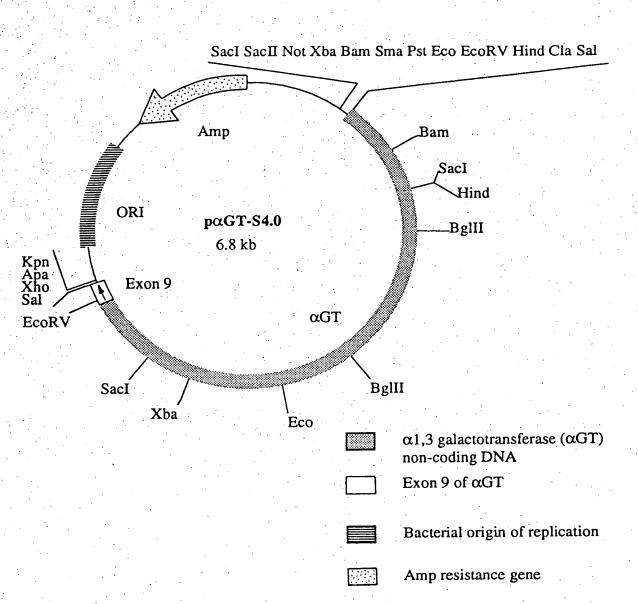
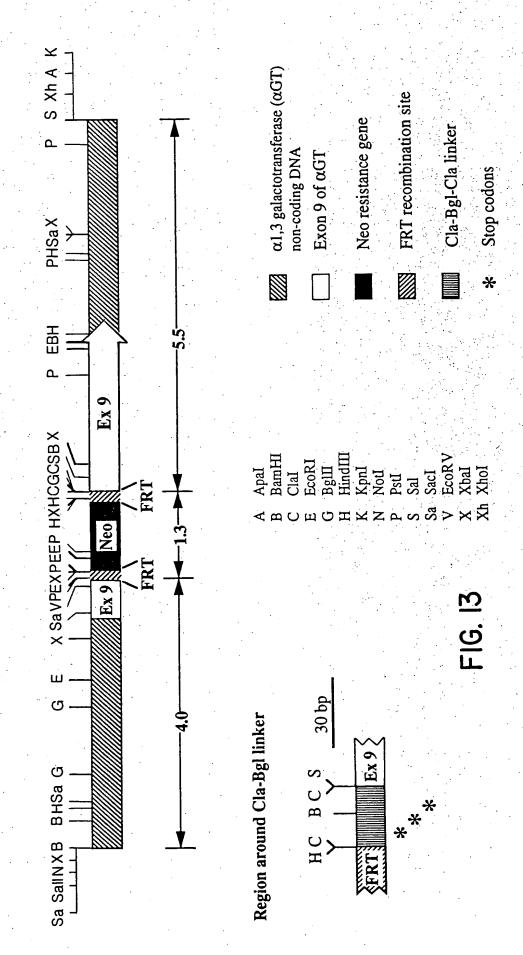


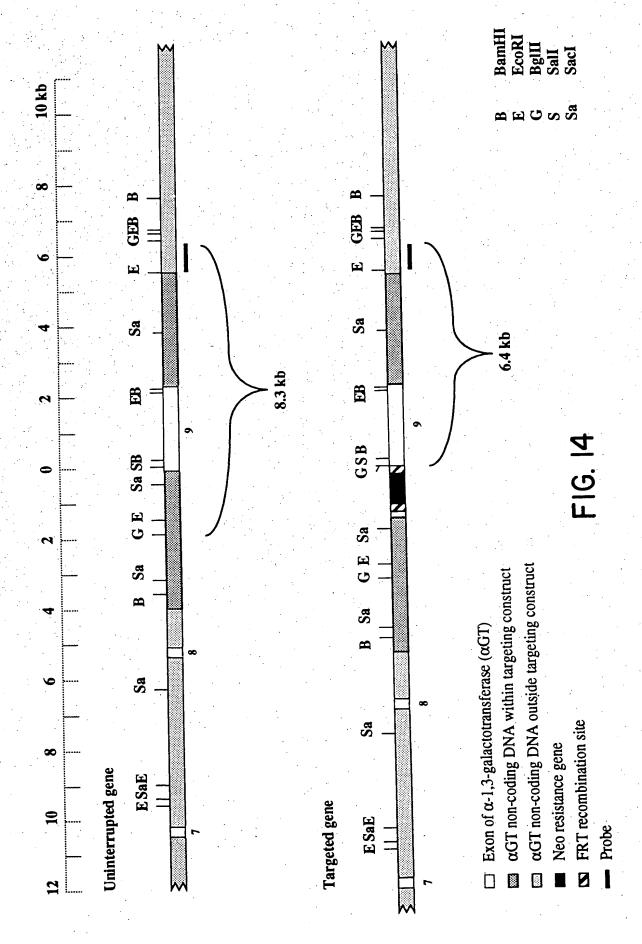
FIG. 12

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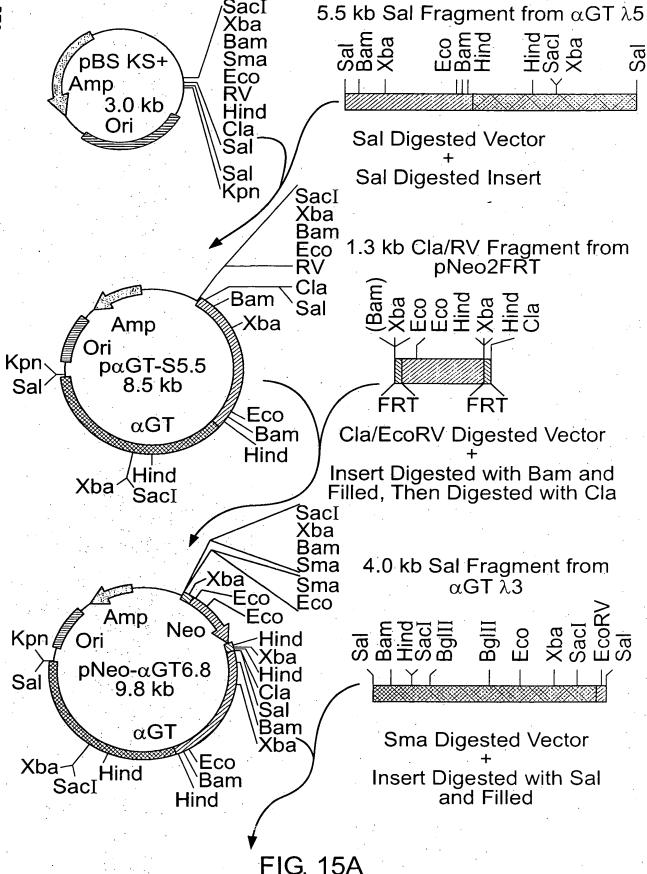
08/984,900 07039-473002



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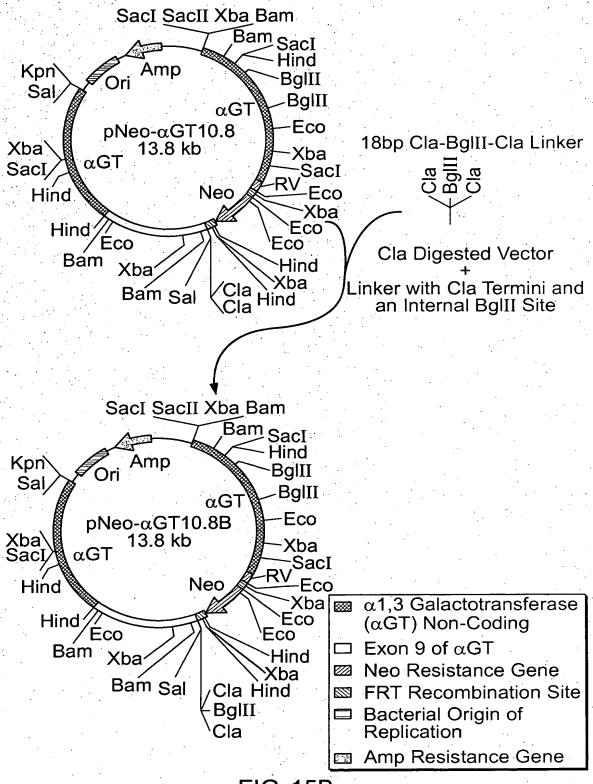


FIG. 15B

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	10	20 -	30	40	50	60
	03.0000000003	CCAAMMCCAM	CATCCCCCAG	COURT A SCOURC	CTATTCCGAA	СТТССТАТТС
	GAGGGCIGCA	GGAATICGAT	GAICCCCCAG	CITOMOTIC	CIMITOGOLLI	
				100	110	120
	70	. 80.	90	100	110	120
	TCTAGAAAGT	ATAGGAACTT	CAAGCTGGGC	TGCAGGAATT	CGATTCGAGC	AGTGTGGTTT
	130	140	150	160	170	180
	TCCAACAGCA	AGCAAAAAGC	CTCTCCACCC	AGGCCTGGAA	TGTTTCCACC	CAATGTCGAG
	IGCAAGAGGA	710C/LLLLLICC				
	100	200	3 210	220	230	240
	190	200	2.10	220	220	AMCMMMCCAC
	CAGTGTGGTT	TTGCAAGAGG	AAGCAAAAAG	CCTCTCCACC	CAGGCCTGGA	AIGITICCAC
•						
	250	260	270	280	290	300
•	CCAATGTCGA	GCAAACCCCG	CCCAGCGTCT	TGTCATTGGC	GAATTCGAAC	ACGCAGATGC
				. 5 %		
	310	320	330	340	350	360
	A CITICOCOCOCO	CCCCCCTCCC	ACCUCC ACUT	СССАТАТТАА	GGTGACGCGT	GTGGCCTCGA
	AG1CGGGGG	GCGCGGTCCC	AGGICCACII	0001111111111		
	252	300	300	400	410	420
	370	380	390	400		3.000C2.CCC2
	ACACCGAGCG	ACCCTGCAGC	CAATATGGGA	TCGGCCATTG	AACAAGATGG	ATTGCACGCA
			11.1	*		
	430	440	450	460	470	480
	CCTTCTCCGG	CCGCTTGGGT	GGAGAGGCTA	TTCGGCTATG	ACTGGGCACA	ACAGACAATC
		500	510	520	530	540
	0.000000000000000000000000000000000000	MDCCCCCCM	CDDCCCCCDC	TCACCCCACC	GGCGCCCGGT	Justinian
	GGCTGCTCTG	ATGCCGCCGT	GTTCCGGCTG	TCAGCGCAGG	GGCGCCCGG1	1011111010
				500	F00	600
	550	560	570	580	590	600
	AAGACCGACC	TGTCCGGTGC	CCTGAATGAA	CTCCAAGACG	AGGCAGCGCG	GCTATCGTGG
	610	620	630	640	650	660
	CITCCCCACCA	CCCCCCTTCC	TTCCCCACCT	GTGCTCGACG	TTGTCACTGA	AGCGGGAAGG
				,		<ul> <li>A contract of the contract of the</li></ul>
	670	C00	600	700	710	720
	6/0	000	200000000		መረጥር አጥርጥር እ	ССФФССФССФ
,	GACTGGCTGC	TATTGGGCGA	AGTGCCGGGG	CAGGATCTCC	TGTCATCTCA	CCIIGCICCI
				<u>.</u>		700
	730	740	750	760	770	780
	GCCGAGAAAG	TATCCATCAT	GGCTGATGCA	ATGCGGCGGC	TGCATACGCT	TGATCCGGCT
				**		
	790	800	810	820	830	840
	A COMPOCE A M	TCCACCACCA	ACCCAAACAT	CCCATCGAGO	GAGCACGTAC	TCGGATGGAA
	ACCIGCCCAI		•		An artist of the second of the second of the	
	250	0.00	970	990	1 890	900
	850	860	. 870	000	, , , , , , , , , , , , , , , , , , , ,	CCCACCCCAA
•	GCCGGTCTTG	TCGATCAGGA	TGATCTGGAC	GAAGAGCATC	AGGGGCTCGC	GCCAGCCGAA
	and the second second		* *	,		
	910	920	930	940	) 950	960
	CTCTTCCCCA	GGCTCAAGGC	GCGGATGCCC	GACGGCGAGG	ATCTCGTCGT	GACCCATGGC
			• .			
	070	000	990	1000	1010	1020
	9/0	70U	ייני מיני בייני	. 3 3 TYCC C C C C C	հասարանը արարական և 	САТССАСТСТ
	GATGCCTGCT	TGCCGAATAT	CHIGGIGGAP	AMIGGCOC.	LITCIGGAIL	CATCGACTGT
·						1000
	1030	1040	1050	1060	1070	1080
	GGCCGGCTGG	GTGTGGCGGA	CCGCTATCAC	GACATAGCG'	TGGCTACCC	TGATATTGCT
	1090	1100	1110	112	0 1130	1140
	CANCACCOOK	GCGCCG ATTC	CCCTCACCC	TTCCTCGTG	C TTTACGGTAT	CGCCGCTCCC
	GAMONGCIIG	GCGGCGWIG	SOCIONCOC			
					•	



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1200	1190	1180	1170	1160	1150
GGATCGGCAA	TCTTCTGAGG	CTTGACGAGT	CTATCGCCTT	GCATCGCCTT	GATTCGCAGC
1260	1250	1240	1230	1220	1210
AAGCTTGAAG	TCGGATCATC	GGGCGTTTGT	CACGGGTGTT	GAATAAAACG	TAAAAAGACA
1320	1310	1300	1290	1280	1270
					TTCCTATTCC
	1370			1340	
				CGATACCGTC	AGATCTTGAT

Linker sequences: 0-28

FRT: 29-104

Polyoma virus enhancer repeats: 105-249

Herpes Simplex Virus Tyrosine Kinase promoter: 250-385

Neomycin phosphotransferase coding region: 385-1188

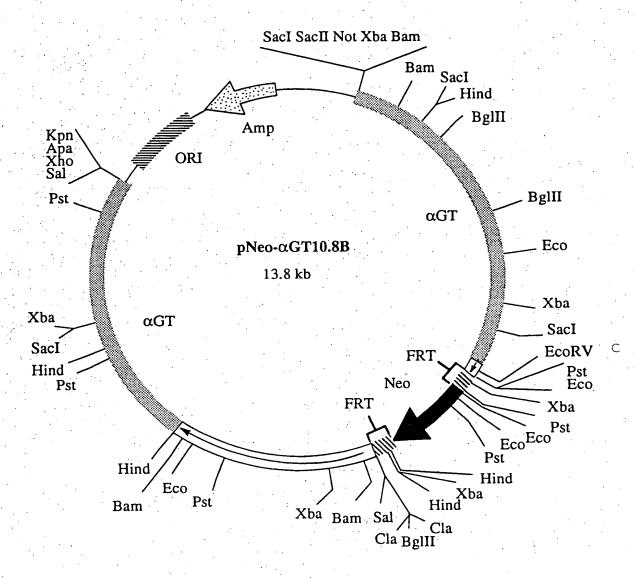
Herpes Simplex Virus Tyrosine Kinase PolyA signal: 1189-1249

FRT: 1250-1310

Linker sequences: 1311-1340

FIG. 16B

07039-473002



α1,3 galactotransferase (αGT) non-coding DNA
 Exon 9 of αGT
 Neo resistance gene
 FRT recombination site
 Bacterial origin of replication
 Amp resistance gene

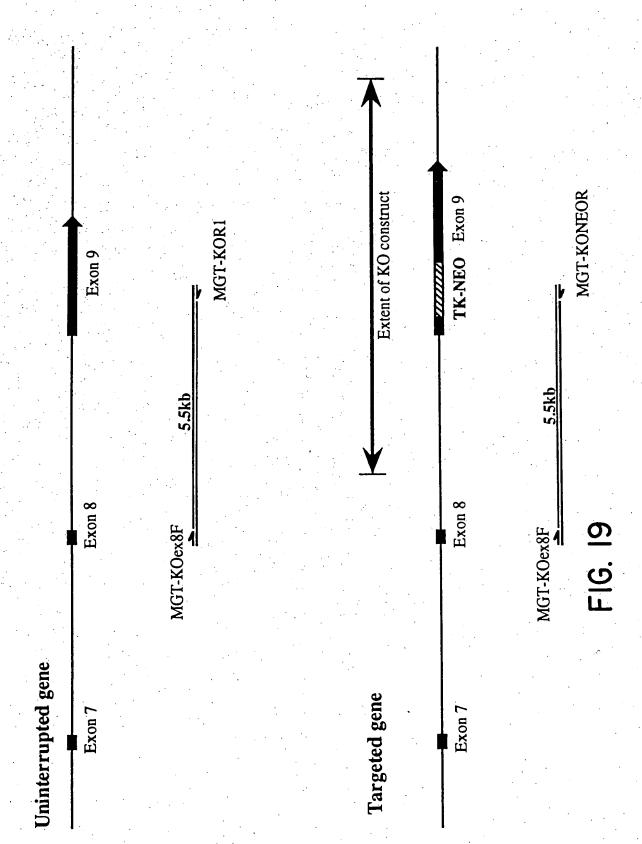
FIG. 17

\_wild-type gene \_disrupted gene

FIG. 18



.4kb



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1234

5.5kb galT PRODUCT

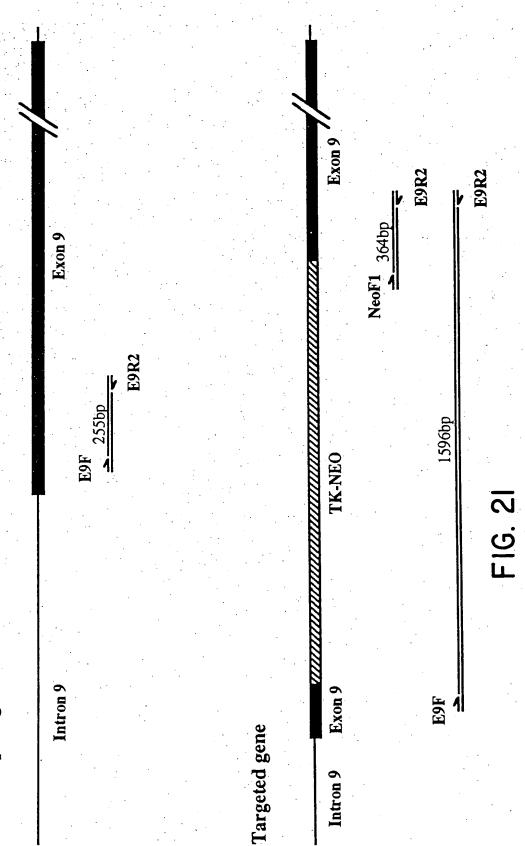


5.5kb KO PRODUCT

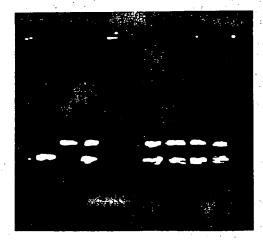
- I. CBAC TEMPLATE; WILD TYPE PRIMERS
- 2. 7C2 TEMPLATE; WILD TYPE PRIMERS
- 3. CBAC TEMPLATE; KO PRIMERS
- 4. 7C2 TEMPLATE; KO PRIMERS

FIG. 20

Uninterrupted gene



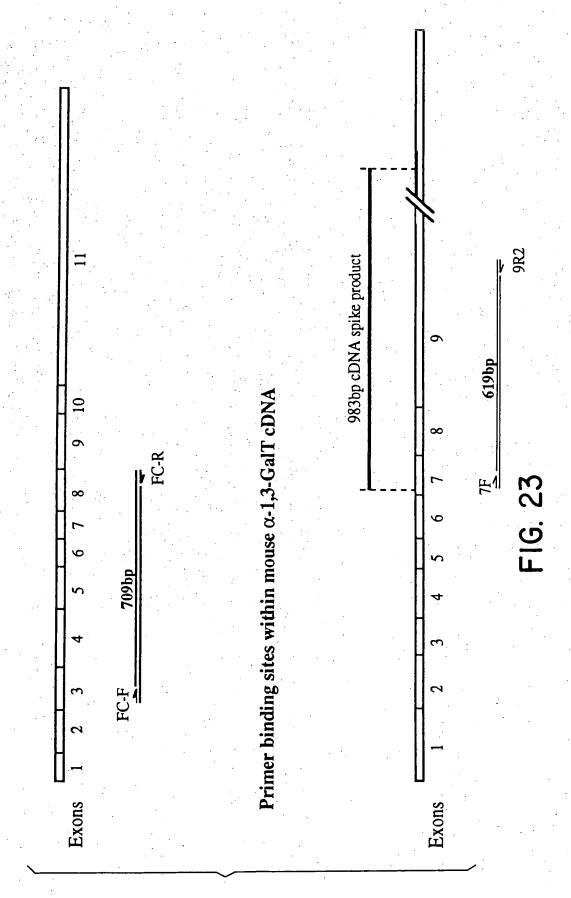
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364bp 255bp

FIG. 22

Primer binding sites within mouse ferrochelatase cDNA



M C K H L K H L M K H L

i) Ferrochelatase, FC-F/R

M, Marker SPP-I C, MQW control K, KIDNEY H, HEART L, LIVER

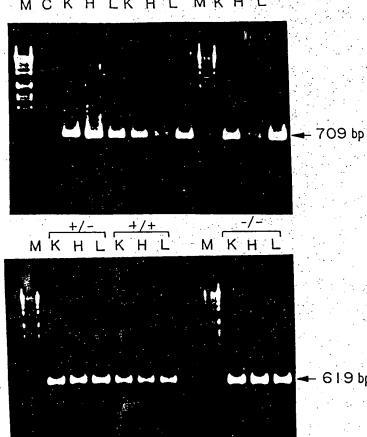
FIG. 24a

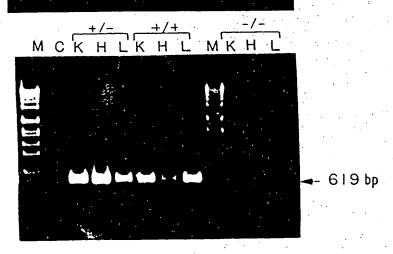
ii) α-1,3-GT cDNA spike + 7F/9R2 primers

FIG. 24b

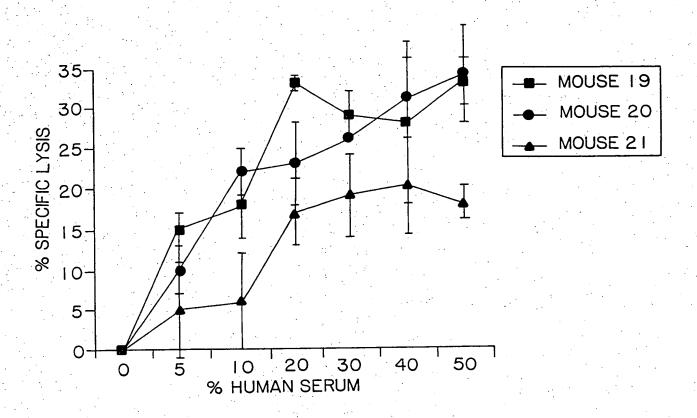
iii) α-1,3-GT 7F/9R2 primers

FIG. 24c





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MOUSE 19: WILD TYPE; MOUSE 20: HETEROZYGOTC Gal KO; MOUSE 21: HOMOZYGOUS Gal KO

FIG. 25

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T-LIF SEQUENCE - Murine

CTGACACCTTTCGCTTTCCTCTTGCGTGTCCGCCTGCGACCTTTCCCCACCCC

GGCCTCTTTCCTGGTTGCACCACTTCCTCTCATTCCAAAGGATTGTGCCCTTA

CTGCTGCTGGTTCTGCACTGGAAACACGGGGCAGGGAGCCCTCTTCCCATCAC

CCCTGTAAATGCCACCTGTGCCATACGCCACCCATGCCACGGCAACCTC

Met Asn Gln Ile Lys Asn Gln Leu Ala Gln Leu Asn Gly ATG AAC CAG ATC AAG AAT CAA CTG GCA CAG CTC AAT GGC

Ser Ala Asn Ala Leu Phe Ile Ser Tyr Tyr Thr Ala Gln Gly AGC GCC AAT GCT CTC TTC ATT TCC TAT TAC ACA GCT CAA GGX

Glu Pro Phe Pro Asn Asn Val Glu Lys Leu Cys Ala Pro Asn GAG CCG TTT CCC AAC AAC GTG GAA AAG CTA TGT GCG CCT AAC

Met Thr Asp Phe Pro Ser Phe His Gly Asn Gly Thr Glu Lys ATG ACA GAC TTC CCA TCT TTC CAT GGC AAC GGG ACA GAG AAG

Thr Lys Leu Val Glu Leu Tyr Arg Met Val Ala Tyr Leu Ser ACC AAG TTG GTG GAG CTG TAT CGG ATG GTC GCA TAC CTG AGC

Ala Ser Leu Thr Asn Ile Thr Arg Asp Gln Lys Val Leu Asn GCC TCC CTG ACC AAT ATC ACC CGG GAC CAG AAG GTC CTG AAC

Pro Thr Ala Val Ser Leu Gln Val Lys Leu Asn Ala Thr Ile CCC ACT GCC GTG AGC CTC CAG GTC AAG CTC AAT GCT ACT ATA

Asp Val Met Arg Gly Leu Leu Ser Asn Val Leu Cys Arg Leu GAC GTC ATG AGG GGC CTC CTC AGC AAT GTG CTT TGC CGT CTG

Cys Asn Lys Tyr Arg Val Gly His Val Asp Val Pro Pro Val TGC AAC AAG TAC CGT GTG GGC CAC GTG GAT GTG CCA CCT GTC

Pro Asp His Ser Asp Lys Glu Ala Phe Gln Arg Lys Lys Leu CCC GAC CAC TCT GAC AAA GAA GCC TTC CAA AGG AAA AAG TTG

Gly Cys Gln Leu Leu Gly Thr Tyr Lys Gln Val Ile Ser Val GGT TGC CAG CTT CTG GGG ACA TAC AAG CAA GTC ATA AGT GTG

Val Val Gln Ala Phe \*\*\*

GTG GTC CAG GCC TTC TAG AGAGGAGGTCTTGAATGTACCATGGACTG.



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GACCTTTTGC CTTTTCTCTC TCCTGGTGCA CCATTTCCTC	TCCCTCCCTG 50
AGCCGGAGTT GTGCCCCTGC TGTTGGTTCT GCACTGGAAA	CATGGGGCGG 100
GGAGCCCCCT CCCCATCACC CCTGTCAACG CCACCTGTGC	CATACGCCAC 150
CCATGTCACA ACAACCTC ATG AAC CAG ATC	182
Met Asn Gln Ile	
AGG AGC CAA CTG GCA CAG CTC AAT GGC AGT GCC	C AAT GCC CTC 227
Arg Ser Gln Leu Ala Gln Leu Asn Gly Ser Ala	a Asn Ala Leu
5 10 15	
TTT ATT CTC TAT TAC ACA GCC CAG GGG GAG CCC	TTC CCC AAC 272
Phe Ile Leu Tyr Tyr Thr Ala Gln Gly Glu Pro	Phe Pro Asn
20 25	30
AAC CTG GAC AAG CTA TGT GGC CCC AAC GTG ACG	GAC TTC CCG 317
Asn Leu Asp Lys Leu Cys Gly Pro Asn Val Thr	Asp Phe Pro
35 40	45
CCC TTC CAC GCC AAC GGC ACG GAG AAG GCC AAG	G CTG GTG GAG 362
Pro Phe His Ala Asn Gly Thr Glu Lys Ala Lys	Leu Val Glu
50 55	60
CTG TAC CGC ATA GTC GTG TAC CTT GGC ACC TCC	CTG GGC AAC 407
Leu Tyr Arg Ile Val Val Tyr Leu Gly Thr Ser	Leu Gly Asn
65 70	
ATC ACC CGG GAC CAG AAG ATC CTC AAC CCC AGT	GCC CTC AGC 452
Ile Thr Arg Asp Gln Lys Ile Leu Asn Pro Ser	· Ala Leu Ser
75 80 85	
CTC CAC AGC AAG CTC AAC GCC ACC GCC GAC ATC	C CTG CGA GGC 497
Leu His Ser Lys Leu Asn Ala Thr Ala Asp Ile	•
90 95	100
CTC CTT AGC AAC GTG CTG TGC CGC CTG TGC AGC	C AAG TAC CAC 542
Leu Leu Ser Asn Val Leu Cys Arg Leu Cys Ser	Lys Tyr His
105 110	115
GTG GGC CAT GTG GAC GTG ACC TAC GGC CCT GAC	C ACC TCG GGT 587
Val Gly His Val Asp Val Thr Tyr Gly Pro Asp	
120 125	130
AAG GAT GTC TTC CAG AAG AAG AAG CTG GGC TGT	CAA CTC CTG 632
Lys Asp Val Phe Gln Lys Lys Lys Leu Gly Cys	•
135 140	
GGG AAG TAT AAG CAG ATC ATC GCC GTG TTG GCC	C CAG GCC TTC 677
Gly Lys Tyr Lys Gln Ile Ile Ala Val Leu Ala	
145 150 155	
TAG CAGGAGGTCT	722
***	

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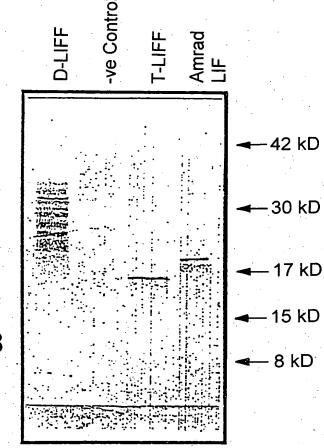


FIG. 28

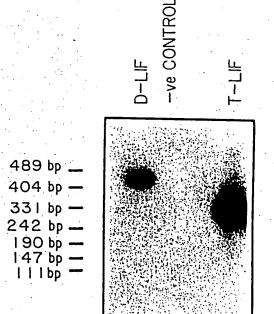
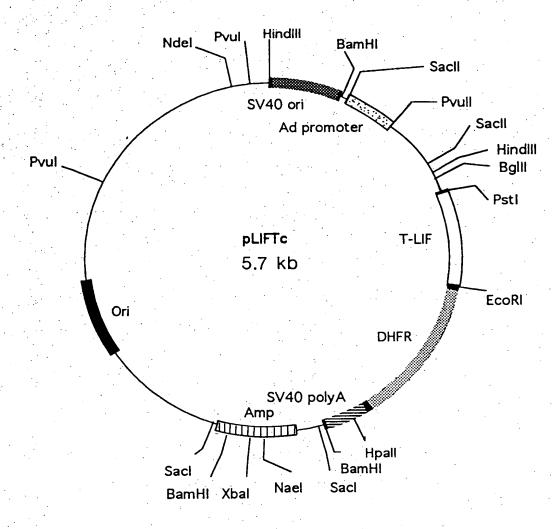


FIG. 30



Dihydrofolate reductase 3' end

Adenovirus promoter

SV40 origin of replication

T-LIF coding region

Bacterial origin of replication

Ampicillin resistance gene

FIG. 29